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Synthesis of (3*S*,3*S*′,4*S*,4*S*′)-1,1′-ethylenedipyrrolidine-3,3′,4,4′-tetraol and related diamino diols: donor–acceptor hydrogen-bonding motifs of the C_2 symmetric 3,4-dihydroxypyrrolidine unit

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Abstract—Enantiopure 1,1′-ethylenedipyrrolidines possessing 3,4-disubstitution have been prepared from esters of L-(+)-tartaric acid. Although diacylation routes via the diacetoxypyrrolidin-2,5-diones were problematic, *N*,*N*-dialkylation protocols proved to be reliable and led to the synthesis of (3*S*,3*S*′,4*S*,4*S*′)-1,1′-ethylenedipyrrolidine-3,3′,4,4′-tetraol, (3*R*,3′*S*,4*R*,4′*S*)-3,4-diamino-1,1′-ethylenedipyrrolidine-3′,4′-diol and (3*R*,3′*R*,4*S*,4′*S*)-3,3′-diamino-1,1′-ethylenedipyrrolidine-4,4′-diol. The tetraol possesses a crystal structure that exhibits an unusual zig-zag intermolecular pattern comprising a network of hydrogen bonds involving the terminal hydroxyl groups and a nitrogen atom of one of the pyrrolidine rings.

1. Introduction

Hydroxylated pyrrolidines and their related fused systems form an important group of natural products,[1] many possessing significant pharmacological properties, including the inhibition of glycosidases.[2] The proximity of stereochemically defined oxygen and nitrogen atoms would be expected to give rise to specific patterns of hydrogen bonding[3,4] that could be involved with biological molecular recognition.[5,6] Such is the case for racemic *trans*-1,2-cyclohexanediol, which gives a crystalline 1:1 adduct when heated with (1*R*,2*R*)-(−)-cyclohexane-1,2-diamine.[7,8]

Within this class, *trans*-3,4-dihydroxypyrrolidines have found several uses including the formation of dendrimers,[9a] the assembly of oligomeric macrocycles[9b] and their action as catalysts in enantioselective alkylations,[9c] functions that make use of their C_2 symmetry. The linking of *trans*-3,4-disubstituted pyrrolidines by an ethylene unit permits the coordination of a metal to both nitrogen atoms, and *trans*-3,4-disubstituted pyrrolidines have been studied as catalysts for asymmetric dihydroxylation by Koga et al.[10] Given the distinctive features of such linked *trans*-3,4-dihydroxypyrrolidines, we sought to devise routes to systems such as **1** and their related diamino diols (Fig. 1).

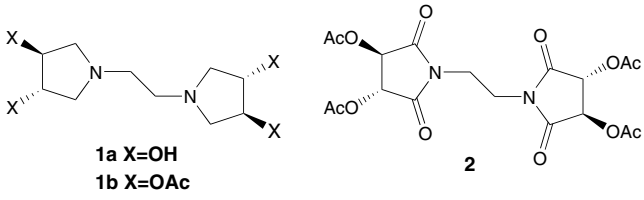

Figure 1.

2. Results and discussion

A succinct route to 1,1′-ethylenedipyrrolidines **1** could involve reduction of the imide **2** derived by *N*,*N*′-dialkylation of (3*R*,4*R*)-diacetoxypyrrolidin-2,5-dione, itself available from L-(+)-tartaric acid by reaction with acetic anhydride followed by treatment with ammonia and cyclisation with acetyl chloride.[11] However, (3*R*,4*R*)-diacetoxypyrrolidin-2,5-dione did not furnish any imide **2** when heated with 1,2-dibromoethane in DMF at up to 100 °C. (3*R*,4*R*)-Diacetoxypyrrolidin-2,5-dione reacted

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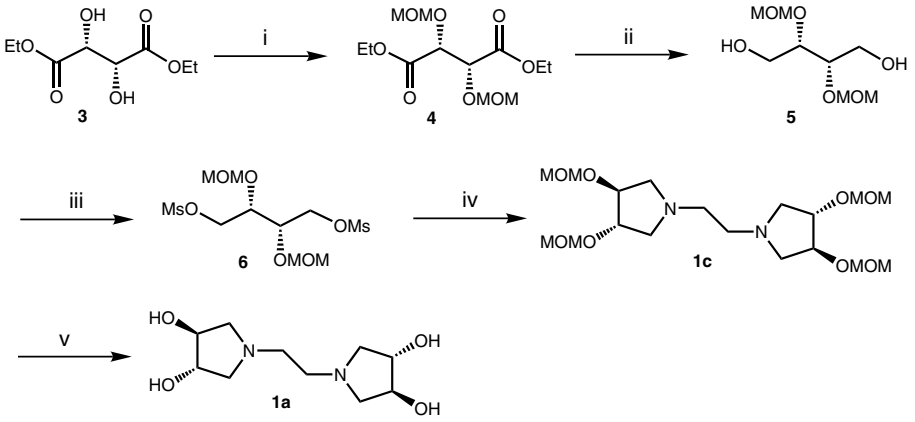


Scheme 1. Reagents and conditions: (i) dimethoxymethane, P_2O_5, $CHCl_3$; (ii) $LiAlH_4$, Et_2O, reflux; work-up with aq NaOH (4 M) 0–20 °C; (iii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (iv) ethylenediamine, K_2CO_3, KI (cat.), 18-crown-6 in DMF at 100 °C; (v) 1:1 hydrochloric acid (10 M)/methanol, 20 °C; then Me_2NEt, −20 to 20 °C.

with ethylene glycol under Mitsunobu conditions (Ph_3P, diethyl diazocarboxylate) to give the imide **2** (17%), but attempted reduction to give either **1a** (X = OH) or **1b** (X = Ac) by either $THF{\cdot}BH_3$ or $NaBH_4$–I_2 in THF[12] was unsuccessful. A dialkylation approach was therefore considered (Scheme 1).

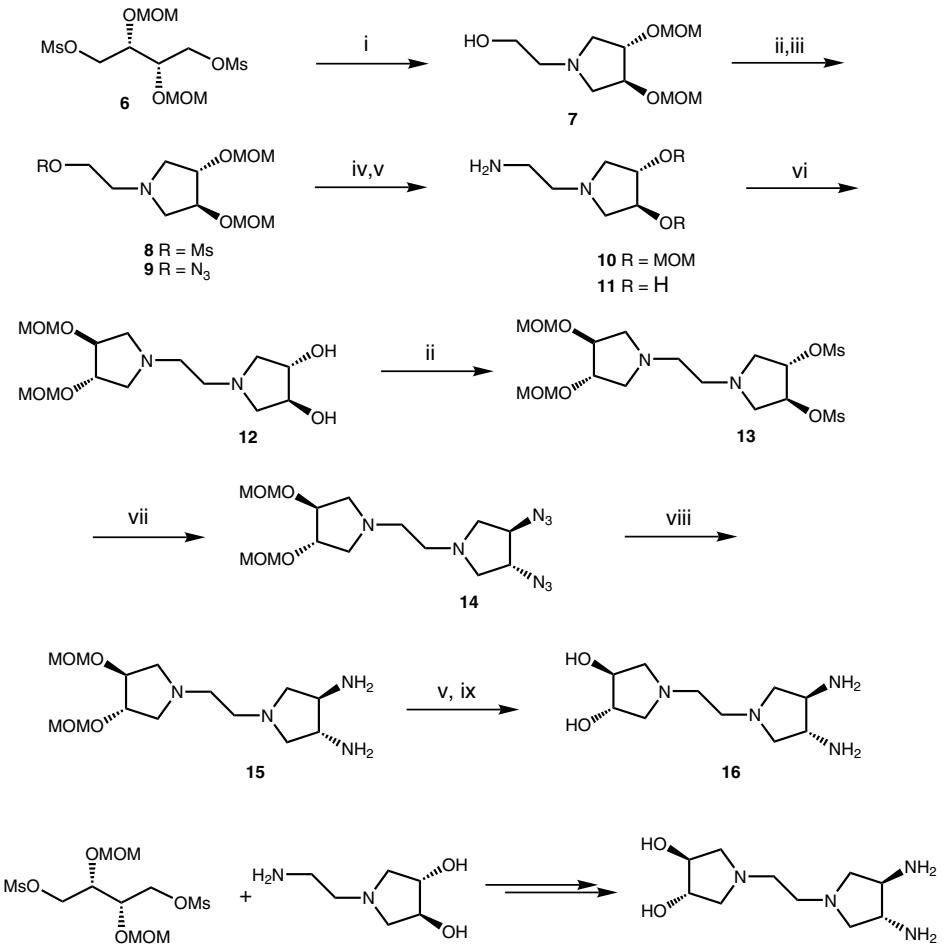
Reaction of (+)-diethyl L-tartrate **3** with 2,2-dimethoxymethane and P_2O_5 in chloroform (Scheme 1) afforded the bis-MOM derivative **4** (74%),[13] which was reduced with $LiAlH_4$ at reflux in diethyl ether to give diol **5**, which was converted into dimesylate **6** in 49% yield by reaction with methanesulfonyl chloride (2.5 equiv) and Et_3N (2.5 equiv). Reaction of dimesylate **6** with ethylenediamine and K_2CO_3 in the presence of catalytic amounts of KI and 18-crown-6 in DMF at 100 °C afforded the 1,1′-ethylenedipyrrolidine **1c** (22%), which was deprotected using 1:1 hydrochloric acid (10 M)/methanol at 20 °C followed by Me_2NEt and then continuous extraction with 1:3 THF/chloroform to give diamino diol **1a** in 55% yield.

The ability of amines to form adducts with alcohols[7,8] suggested that the terminal groups of diamino diol **16** could lead to interesting non-covalent interactions, and a synthesis was devised (Scheme 2). Dimesylate **6** underwent cyclisation with ethanolamine in the presence of $KHCO_3$ to give 1-(2-hydroxyethyl)pyrrolidine **7** in 57% yield, which was converted into the unstable mesylate **8** (50%) with methanesulfonyl chloride (1.5 equiv) and Et_3N (1.5 equiv) in dichloromethane at −30 °C. Mesylate **8** was treated with NaN_3 (2 equiv) in DMF at 80 °C for 16 h, giving azide **9** (54%), which was hydrogenated over 10% palladium on carbon in ethanol to give amine **10** (82%). Deprotection using 1:1 10 M HCl/MeOH afforded **11** (51%), which was condensed with dimesylate **6** using $KHCO_3$ as the base and in the presence of catalytic amounts of KI and 18-crown-6 in DMF at 100 °C to give diol **12** (31%). Mesylation of **12** with methanesulfonyl chloride (3 equiv) and Et_3N (3 equiv) in dichloromethane from 0 to 20 °C proceeded in 46% yield to give dimesylate **13**, which underwent twofold displacement with LiN_3 (10 equiv) in DMF at 80 °C for 48 h, giving diazide **14** (56%), which was hydrogenated over 10% palladium on carbon in ethanol to give diamine **15** (73%). The MOM groups of **15** were cleaved with concd hydrochloric acid and methanol prior to neutralisation with Me_2NEt, furnishing diamino diol **16** in 10% yield.

It was also of interest to prepare ethylene-linked pyrrolidines that contain an amino alcohol unit on each ring (Scheme 3). The approach to amino alcohol **22** employed the attack of an azide on the cyclic sulfate **19**, a protocol developed by Gao and Sharpless.[14] Making use of known procedures,[15–17] L-(+)-tartaric acid was converted into diol **17**, which upon treatment with $SOCl_2$ and a catalytic amount of DMF in dichloromethane afforded the sulfite **18**. Oxidation of **18** using $NaIO_4$ in the presence of a catalytic amount of RuO_2 in 2:1 acetonitrile/water afforded the desired cyclic sulfate **19** (43%), which with NaN_3 (5 equiv) in 1:1 aqueous acetone at 25 °C afforded azido dimesylate **20** (67%) after careful acidification. Condensation of dimesylate **20** with ethylenediamine, in the presence of $KHCO_3$ and a catalytic amount of 18-crown-6 in DMF at 100 °C afforded diazide **21** (12%), which on treatment with hydrogen at 1 atm over 10% palladium on carbon in ethanol afforded diamino diol **22** in 23% yield. Other routes were unsuccessful, including an attempt to proceed via **23**, obtained from (+)-dimethyl L-tartrate via the Gao-Sharpless procedure,[14] but which could not be reduced satisfactorily by $LiAlH_4$ in THF at reflux to give the key amine intermediate **24**.

2.1. Crystallisation studies

After Kawashima and Hirayama's discovery that heating (1*R*,2*R*)-(−)-cyclohexane-1,2-diamine with racemic *trans*-1,2-cyclohexanediol gave a crystalline adduct of 1:1 stoichiometry,[1] Hanessian et al. showed that such adducts possess remarkable ordering as triple helicate systems with a polar core and hydrophobic periphery.[8] The mode of helicity depends upon the absolute configuration of the diamine. Such molecular recognition of a primary amine by an alcohol is consistent with



Scheme 2. Reagents and conditions: (i) $H_2NCH_2CH_2OH$, KI (cat.), K_2CO_3, 18-crown-6, in DMF, 100 °C, 48 h; (ii) $MeSO_2Cl$, Et_3N, in dichloromethane, 0 °C, 1 h to give **8**; 20 °C, 45 min for **13**; (iii) NaN_3, DMF, 80 °C, 16 h for **9**; 100 °C for **14**; (iv) H_2 10% Pd–C, EtOH, 20 °C; (v) 1:1 10 M HCl/MeOH, 20 °C, 16 h; (vi) **6**, $KHCO_3$, KI (cat.), 18-crown-6 (cat.) in DMF, 100 °C, 48 h; (vii) LiN_3, DMF, 80 °C, 48 h; (viii) H_2 (1 atm), 10% Pd–C, ethanol, 20 °C; (ix) 1:1 hydrochloric acid (10 M)/methanol, 20 °C; then Me_2NEt, −20 to 20 °C.

the lone pair of the amino group acting as an acceptor, the two hydrogen atoms being available as donors; whereas for an alcohol, the two lone pairs can be acceptors but only one donor (the hydrogen atom) is available.[3,8] Thus, in a 1:1 stoichiometry of the cyclohexane-1,2-diamine with *trans*-1,2-cyclohexanediol, the donor–acceptor ratio is balanced, and a stable adduct could be expected in the absence of other factors, including adverse stereochemistry.

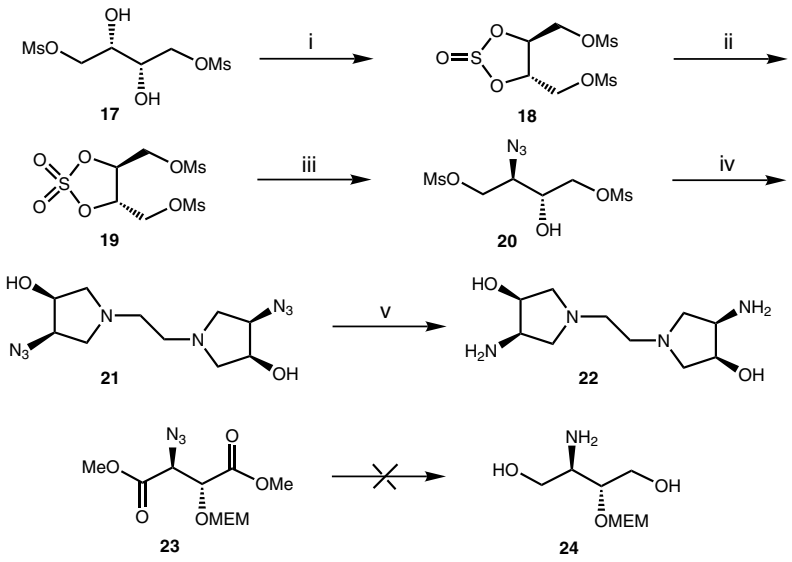
Such analysis would be expedited by the knowledge of the tertiary amine–alcohol interactions in the symmetrical tetraol **1a**. Crystallisation of **1a** from methanol–chloroform by slow diffusion afforded rhombic needles whose structure was determined by single crystal X-ray diffraction[18] (Fig. 2). The trans-disposition of the two hydroxy groups appended to pyrrolidine rings in envelope conformations is apparent.

An interesting supramolecular architecture was observed (Fig. 3), in which a strong hydrogen-bonding array[19] is formed between the alcohol moieties [O1···O2, and O3···O4 = 1.9514(4) Å] in addition to a single, slightly weaker, alcohol–amine interaction [O1···N1 = 2.0031(5) Å]. This produces a two-dimensional network of extended zig-zag (or herring-bone) sheets, with the sheets being stacked in parallel layers, which are bound by means of two weaker, inter-layer, hydrogen bonds (O2···C1, C7···O4 = 2.4209(3) and 2.5442(2) Å, respectively).

The above considerations of donor:acceptor ratios imply that the 1:1 amine/alcohol complementarity exists in diamino diol **16**, assuming that the tertiary nitrogen atoms are not engaged in hydrogen bonding. Such complementarity is observed in the 1:1 adduct of racemic *trans*-1,2-cyclohexanediol with (1*R*,2*R*)-(−)-cyclohexane-1,2-diamine,[7,8] and by analogy the diamino diol **16** might align in a head-to-tail assembly. However, **16** was obtained as an oil, which resisted several attempts at crystallisation. The *cis*-3,4-amino alcohol units of **22** could also participate in an ordered network of hydrogen bonding;[20] but again, **22** could not be obtained in crystalline form.

3. Conclusions

Enantiopure 1,1′-ethylenedipyrrolidines possessing 3,4-disubstitution have been prepared from esters of



Scheme 3. Reagents and conditions: (i) $SOCl_2$, cat. DMF in dichloromethane, 20 °C; (ii) $NaIO_4$, cat. RuO_2 in 2:1 MeCN/H_2O; (iii) NaN_3, acetone, 25 °C; subsequent addition of 1:1 2 M aq H_2SO_4/ether; (iv) ethylenediamine, $KHCO_3$, 18-crown-6 (cat.) in DMF, 100 °C; (v) H_2 (1 atm), 10% Pd–C, ethanol, 20 °C.

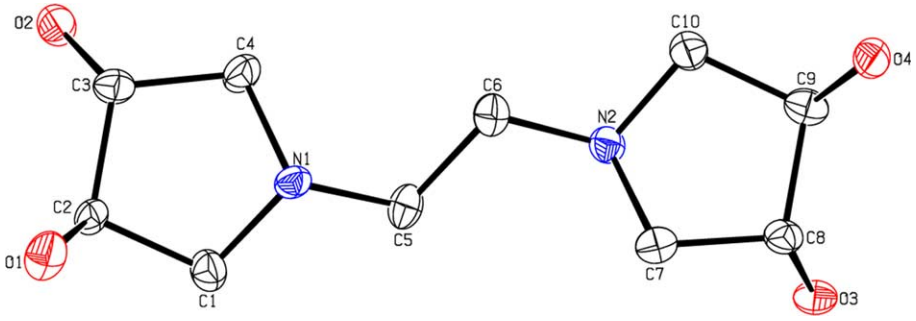


Figure 2. ORTEP structure of (3*S*,3*S*′,4*S*,4*S*′)-1,1′-ethylenedipyrrolidine-3,3′,4,4′-tetraol **1a**.

L-(+)-tartaric acid. Diacylation routes via the diacetoxypyrrolidin-2,5-diones were problematic, but *N*,*N*-dialkylation protocols proved to be reliable and enabled the synthesis of one tetraol and two diamino diol systems, each containing the 1,1′-ethylenedipyrrolidine framework. Previous studies have shown that molecular recognition between amino and hydroxy groups in *different* compounds is possible. Herein, an unusual example of pre-organisation between amino and hydroxy groups in the *same* molecule has been presented. Such studies suggest that other non-planar and hydroxylated *N*-heterocycles may possess interesting features of pre-organisation, and of possible relevance to related natural products and transformations by enzymes.

4. Experimental

4.1. General

Analytical thin-layer chromatography (TLC) was performed on Merck 0.25 mm thick pre-coated, aluminium-backed silica gel plates, visualised by UV illumination or iodine vapour, or developed by charring with one of: (a) 5% anisaldehyde in ethanol/acetic acid/sulfuric acid (95:5:1 by volume), (b) 2% vanillin in ethanol/sulfuric acid (98:2), (c) 1% potassium permanganate in aqueous 0.5 M potassium carbonate or (d) 2.0 M sulfuric acid saturated with cerium(IV) sulfate. Flash column chromatography was performed on alumina (Merck 90, 63–200 μm; 60G neutral type E) or silica gel (Merck 40–63 μm, 230–400 mesh). Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were recorded on an Optical activity AA-100 digital polarimeter using the sodium-D line. ^{1}H NMR spectra were recorded at 250 MHz while ^{13}C NMR spectra were recorded at 62 MHz, both in $CDCl_3$ and on a Bruker AM 250 instrument unless otherwise stated, using tetramethylsilane as the internal standard. ^{19}F NMR spectra were observed on ^{1}H channel de-tune (heteronuclear probe) and were recorded at 565 MHz on a Bruker AMX 600 instrument, or were assigned as ^{1}H coupled or ^{1}H decoupled at 376 MHz. ^{19}F chemical shift values are expressed in parts per million relative to inter-

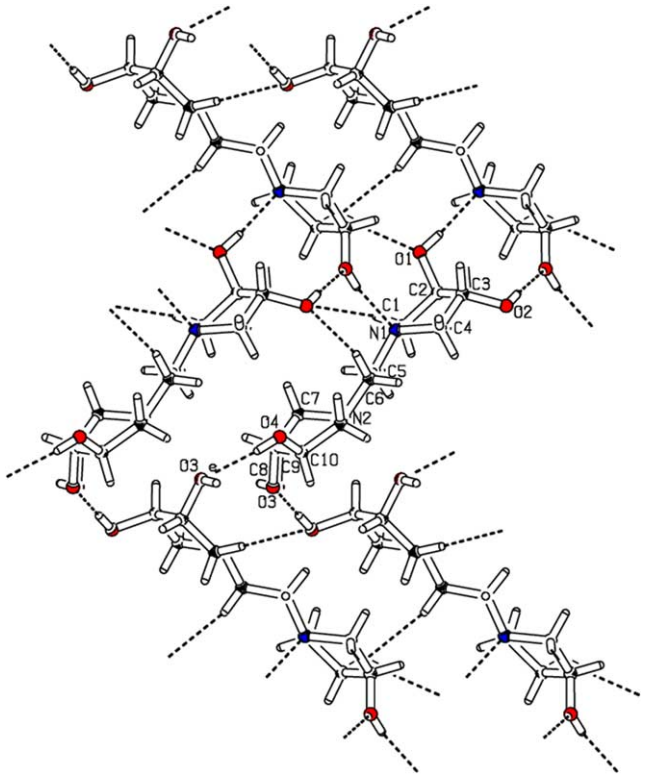


Figure 3. The hydrogen bonded supramolecular architecture of (3*S*,3*S*′,4*S*,4*S*′)-1,1′-ethylenedipyrrolidine-3,3′,4,4′-tetraol **1a**.

nal trichlorofluoromethane. Infra red spectra were recorded as KBr plates, chloroform solution or neat as liquid films. Mass spectra were obtained either as electron impact ($HRMS_{EI}$) or fast atom bombardment ($HRMS_{FAB}$) in a *m*-nitrobenzoic acid (+Na) matrix.

All reactions were performed under an atmosphere of dry nitrogen except for those reactions conducted in aqueous media. Solvents were rigorously dried and purified prior to use. Solvents were transferred via cannulation (stainless steel double-tipped needle) under positive atmospheric pressure. Evaporation of solvent refers to removal under reduced pressure.

The following compounds were prepared according to the literature procedures: (3*R*,4*R*)-3,4-diacetoxypyrrolidin-2,5-dione;[11] diethyl (2*R*,3*R*)-2,3-bis(methoxymethyloxy)butanedioate **4**;[13] (2*S*,3*S*)-2,3-bis(methoxymethyloxy)butane-1,4-diol **5**;[13] (2*S*,3*S*)-1,4-bis(methanesulfonyloxy)butane-2,3-diol **17**;[17] (4*S*,5*S*)-4,5-bis[methyl-(methanesulfonyloxy)]-2-oxo-1,2,3-thiolane **18**.[16]

4.1.1. (3*R*,3′*R*,4*R*,4′*R*)-3,3′,4,4′-Tetrakis(acetoxy)-1,1′-ethylenedipyrrolidine-2,2′,5,5′-dione 2. To a stirred solution of (3*R*,4*R*)-3,4-diacetoxypyrrolidin-2,5-dione[11] (8.0 g, 37.2 mmol), triphenylphosphine (12.2 g, 46.5 mmol) and ethylene glycol (1.15 g, 18.6 mmol) in dry benzene (100 mL) at 0 °C under an atmosphere of dry nitrogen was added dropwise a solution of diethylazido dicarboxylate, (9.71 g, 55.8 mmol) in dry benzene (15 mL) using a stainless steel, double-tipped needle. The mixture was allowed to warm slowly to 20 °C and stirring continued at that temperature for 48 h under an atmosphere of dry nitrogen. Addition of 40–60 °C petroleum ether (100 mL), filtration and evaporation gave a residue that was adsorbed onto silica gel and the impregnated dispersion was applied to the top of a pre-packed column of silica gel, which was eluted with 1:1 ethyl acetate/40–60 °C petroleum ether to give 2 (1.48 g, 17%) as a buff solid, mp 154–158 °C. An analytical sample crystallised from benzene as colourless needles, mp 163–164 °C; $[\alpha]_D^{30} = +70.1$ (*c* 0.95, chloroform); IR ν_{max} (KBr) 3020, 2970, 2930, 1750, 1730 (C=O) cm^{-1}; ^1H NMR δ 5.55 (4H, s, C*H*OAc), 3.86 (4H, dt, *J* 18.0, 9.0 Hz, CH_2CH_2) 2.19 (12H, s, OAc); ^{13}C NMR δ 169.7 ($COCH_3$), 169.6 (NCO), 72.5 (*C*HOAc), 37.2 (CH_2CH_2), 20.3 ($COCH_3$); $LRMS_{FAB}$ *m/e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 457 ($[M+H]^+$, 19), 415 (27), 397 (22), 373 (28), 331 (19), 218 (100), 204 (30). $HRMS_{FAB}$ Calcd for $C_{18}H_{21}N_2O_{12}$ $[M+H]^+$ 457.1094. Found: 457.1088. Anal. Calcd for $C_{18}H_{20}N_2O_{12}$: C, 47.37; H, 4.42; N, 6.14. Found: C, 47.26; H, 4.22; N, 6.01.

4.1.2. General procedure A: (2*S*,3*S*)-2,3-bis(methoxymethyloxy)-4-methylsulfonyloxy-butylmethanesulfonate 6. To a stirred solution of (2*R*,3*R*)-2,3-bis(methoxymethyloxy)butane-1,4-diol **5**[8] (15.0 g, 71.4 mmol) and triethylamine (18.1 g, 179 mmol) in dry dichloromethane (200 mL) at 0 °C under an atmosphere of dry nitrogen was added dropwise a solution of methanesulfonyl chloride (20.5 g, 179 mol) in dry dichloromethane (45 mL), using a double-tipped stainless steel needle. The mixture was stirred at 0 °C under an atmosphere of dry nitrogen for 1 h, then quenched by addition of water (50 mL), and the organic layer was separated and retained. The aqueous layer was extracted with dichloromethane (3×40 mL). The combined dichloromethane extracts were washed sequentially with 50 mL portions of water, 4 M hydrochloric acid and lastly saturated aqueous sodium hydrogen carbonate. The original organic layer was combined with the dichloromethane extracts and the whole washed with brine (2×50 mL) and dried over $MgSO_4$. The solution was filtered through a sintered glass funnel and the filtrate evaporated. The residue was adsorbed onto neutral alumina and the impregnated dispersion was applied to the top of a pre-packed column of silica gel and eluted with ethyl acetate/40–60 °C petroleum ether (gradient elution: 1:1 to 1:0). The appropriate fractions were combined, filtered through a glass wool plug and evaporated to give **6** (12.8 g, 49%) as a pale yellow oil. An analytical sample was obtained by low-temperature recrystallisation (−35 °C) from chloroform giving **6** as needles, mp 89.5–90 °C; $[\alpha]_D^{27} = +10.4$ (*c* 0.25, chloroform); IR ν_{max} (KBr) 2940, 2900, 1350 (S=O) cm^{-1}; ^1H NMR δ 4.74 (2H, d, *J* 7.0 Hz, OC*H*HO), 4.70 (2H, d, *J* 7.0 Hz, OCH*H*O), 4.41 (2H, dd, *J* 10.0, 5.0 Hz, C*H*HOMs), 4.30 (2H, dd, *J* 10.0, 5.0 Hz, CH*H*OMs), 4.02 (2H, t, *J* 5.0 Hz, OCH), 3.38 (6H, s, OMe), 3.04 (6H, s, SO_2Me); ^{13}C NMR δ 97.4 (OCH_2O), 75.0 (CH_2OMs), 68.1 (CH), 56.2 (OMe), 37.5 (SO_2Me); $LRMS_{EI}$ *m/e* (rel. intensity %) 289 [$C_7H_{13}O_8S_2$, $M^+-C_3H_9O_2$, (3)], 289 (4), 185 (5), 151 (8), 98 (7), 85 (47) and 45 (100); $HRMS_{EI}$ Calcd for $C_7H_{13}O_8S_2$ ($M^+-C_3H_9O_2$) 289.0052. Found: 289.0038.

4.1.3. General procedure B: (3*S*,3*S*′,4*S*,4*S*′)-3,3′,4,4′-tetrakis(methoxymethyloxy)-1,1′-ethylenedipyrrolidine 1c. To a stirred suspension of the methanesulfonate **6** (10.0 g, 27.3 mmol), potassium carbonate (11.3 g, 82.0 mmol), 18-crown-6 (0.72 g, 2.73 mmol) and potassium iodide (0.45 g, 2.73 mmol) in dry DMF (150 mL) at −10 °C under an atmosphere of dry nitrogen was added via a syringe a solution of ethylenediamine (0.91 mL, 0.82 g, 13.7 mmol) in dry triethylamine (3 mL). The mixture was heated slowly to 100 °C and stirred at that temperature for 48 h under an atmosphere of dry nitrogen. The DMF was removed by distillation under reduced pressure and the residue was suspended in saturated aqueous ammonium chloride (150 mL) and the mixture continuously extracted with 3:1 ethyl acetate/2-butanone for 80 h. The organic layer was dried over K_2CO_3, filtered through a sintered glass funnel and the filtrate evaporated. The residue was adsorbed onto neutral alumina and the impregnated dispersion was applied to the top of a pre-packed silica gel column and eluted with 99:1 chloroform/methanol to give **1c** (2.4 g, 22%) as a colourless syrup. An analytical sample was obtained by preparative silica plate thin-layer chromatography (two plate elutions at 20 °C with 99:1 chloroform/acetonitrile). The appropriate band was excised and extracted with methanol, filtered through a sintered glass microfunnel and the filtrate was evaporated under reduced pressure and the residue redissolved in chloroform. This solution was filtered through a fluted paper and the filtrate was evaporated to give **1c** as a colourless syrup; $[\alpha]_D^{30} = -10.6$ (*c* 0.15, chloroform); IR ν_{max} (film) 2940, 2890, 2825, 1450 cm^{-1}; ^1H NMR δ 4.70 (4H, d, *J* 6.5 Hz, OC*H*H), 4.64 (4H, d, *J* 6.5 Hz, OCH*H*), 4.13 (4H, t, *J* 5.0 Hz, OCH), 3.39 (12H, s, OMe), 3.00 (4H, m, NC*H*H), 2.67 (4H, s, CH_2CH_2) and 2.62 (4H, m, NCH*H*); ^{13}C NMR δ 95.8 (OCH_2O), 81.2 (OCH), 59.2 (NCH_2), 55.6 (OMe), 54.6 (CH_2CH_2); $LRMS_{EI}$ *m*/*e* (rel. intensity %) 233 [$C_{17}H_{33}N_2O_7$, M^+-CH_3O (3)], 285 (15), 204 (85), 82 (7.6), 45 (100), 145 (66), 137 (33), 117 (46). $HRMS_{EI}$ Calcd for $C_{17}H_{33}N_2O_7$ (M^+-CH_3O) 377.2288. Found: 377.2278.

4.1.4. (3*S*,3*S*′,4*S*,4*S*′)-1,1′-Ethylenedipyrrolidine-3,3′,4,4′-tetraol 1a. To a stirred suspension of pyrrolidine **1c** (2.20 g, 5.45 mmol) in methanol (10 mL) at 0 °C under an atmosphere of nitrogen was added dropwise concentrated hydrochloric acid (10 mL, 10 M). The mixture was allowed to warm slowly to 20 °C and stirred at that temperature for 48 h under an atmosphere of dry nitrogen. Evaporation gave a residue that was made basic by the addition of *N*,*N*-dimethylethylamine (CAUTION) at −20 °C under an atmosphere of nitrogen with stirring. The mixture was allowed to warm slowly to 20 °C and the digestion continued for 2 h under an atmosphere of nitrogen. Evaporation gave a residue that was suspended in saturated aqueous ammonium chloride (70 mL) and the mixture continuously extracted with 3:1 chloroform/THF for 80 h under an atmosphere of nitrogen. The organic layer was dried over K_2CO_3, filtered through a sintered glass funnel and the filtrate evaporated. The residue was adsorbed onto neutral alumina and the impregnated dispersion was applied to the top of a pre-packed silica gel column and eluted with 99:1 methanol/0.880 aqueous ammonia. The appropriate fractions were filtered and evaporated to give **1a** (0.70 g, 55%) as a yellow oil that slowly solidified upon standing. An analytical sample was obtained by preparative silica plate thin-layer chromatography (three plate elutions with 9:1 methanol/acetonitrile at 5 °C in the dark; extraction and isolation as in General procedure B) to give **1a** as a white amorphous solid, mp 164–166 °C. Recrystallisation from methanol by the slow diffusion of chloroform vapour at 5 °C gave **1a** as long white needles, mp 168 °C; $[\alpha]_D^{30} = +15.4$ (*c* 0.35, methanol); IR ν_{max} (KBr) 3320 (OH), 2930, 2820 cm^{-1}; ^1H NMR (CD_3OD) δ 4.79 (4H, s, CHO*H*), 3.98 (4H, t, *J* 6.0, 4.5 Hz, C*H*OH), 2.93 (4H, dd, *J* 10.0, 6.0 Hz, NC*H*H), 2.58 (4H, m, CH_2CH_2), 2.50 (4H, dd, *J* 10.0, 4.5 Hz, NCH*H*); ^{13}C NMR (CD_3OD) δ 79.0 (CHOH), 61.9 (NCH_2), 56.0 (CH_2CH_2); $LRMS_{EI}$ *m*/*e* (rel. intensity %) 119 (24), 117 (87), 116 (100). $HRMS_{EI}$ Calcd for $C_{10}H_{17}N_2O_2$ ($M^+-H_3O_2$) 197.1290. Found: 197.1279.

4.1.5. (3*S*,4*S*)-1-(2-Hydroxyethyl)-3,4-bis(methoxymethyloxy)pyrrolidine 7. To a stirred suspension of the methanesulfonate **6** (13.0 g, 35.5 mmol), potassium carbonate (14.7 g, 107 mmol), 18-crown-6 (0.89 mg, 3.5 mmol) and potassium iodide (0.59 g, 3.5 mmol) in dry DMF (120 mL) at −10 °C under an atmosphere of dry nitrogen was added via a syringe a solution of ethanolamine (2.14 mL, 2.16 g, 35.5 mmol) in dry triethylamine (3 mL). The mixture was slowly heated with stirring to 100 °C and maintained at that temperature for 48 h under an atmosphere of dry nitrogen. Removal of DMF, extraction and work-up as in General procedure B gave a gum that was purified by short-path distillation (bp 190–196 °C/1.2 mmHg). The resulting glassy solid was adsorbed onto neutral alumina and the impregnated dispersion applied to the top of a prepacked silica gel column and eluted with 49:1 chloroform/methanol to give **7** (4.76 g, 57%) as a yellow gum. An analytical sample was obtained by preparative silica plate thin-layer chromatography (two plate elutions with chloroform and isolation as described in General procedure B) to give **7** as a viscous oil; $[\alpha]_D^{31} = -0.8$ (*c* 0.5, methanol); IR ν_{max} (film) 3420 (OH), 2940, 2890 cm^{-1}; ^1H NMR δ 4.64 (2H, d, *J* 7.5 Hz, OC*H*HO), 4.58 (2H, d, *J* 7.5 Hz, OCH*H*O), 4.07 (2H, *J* 4.0 Hz, OCH), 3.56 (2H, t, *J* 5.5 Hz, NCH_2CH_2), 3.30 (6H, s, OMe), 2.92 (2H, dd, *J* 10.0, 7.0 Hz, NC*H*H), 2.7 (1H, br, CH_2OH), 2.56 (2H, m, NCH_2CH_2 and 2H, dd, *J* 11.0, 5.0 Hz, NCH*H*); ^{13}C NMR δ 95.8 (OCH_2O), 81.5 (OCH), 59.7 (NCH_2CH_2), 58.7 (NCH_2CHO), 57.8 (NCH_2CH_2), 55.5 (OMe); $LRMS_{EI}$ *m*/*e* (rel. intensity %) 235 (M^+, 1.1), 206 (10), 204 (100), 160 (4), 86 (5), 45 (65). $HRMS_{EI}$ exact mass calcd for $C_{10}H_{21}NO_5$ (M^+) 235.1420. Found: 235.1420.

4.1.6. Procedure C: (3*S*,4*S*)-1-[2-(methanesulfonyloxy)-ethyl]-3,4-bis(methoxymethyloxy)pyrrolidine 8. To a stirred solution of pyrrolidine **7** (25.6 g, 109 mmol) and triethylamine (16.6 g, 164 mmol) in 200 mL of anhydrous dichloromethane at −30 °C under an atmosphere of dry nitrogen was added dropwise a solution of methanesulfonyl chloride (18.8 g, 164 mmol) in 50 mL of dry

dichloromethane using a stainless steel double-tipped needle. The mixture was allowed to warm slowly to 0 °C and stirring continued at that temperature for 1 h under an atmosphere of dry nitrogen. The mixture was quenched by addition of water (100 mL) and the organic layer was separated and retained. The aqueous layer was extracted with dichloromethane (2×50 mL). The combined dichloromethane extracts were washed sequentially with 50 mL portions of water, aqueous 2 M citric acid and then saturated aqueous sodium hydrogen carbonate. The original organic layer was combined with the dichloromethane extracts and the solution was washed with brine (2×50 mL) and dried over $MgSO_4$. The solution was filtered through a sintered glass funnel and the filtrate evaporated. The residue was adsorbed onto neutral alumina and the impregnated dispersion was applied to the top of a pre-packed column of silica gel and eluted in the dark with 9:1 ethyl acetate/40–60 °C petroleum ether pre-cooled to 5 °C. The appropriate fractions were combined, filtered through a glass wool plug and the eluent evaporated to give **8** (15.7 g, 46%) as a dark solid. An analytical sample was obtained by preparative silica plate thin-layer chromatography (with toluene at 5 °C in the dark followed by extraction and isolation as in General procedure B) to give **8** as an oil. For spectral analysis, this material was dissolved in C_6D_6 and passed rapidly through a Pasteur pipette containing 2 cm of alumina; $[\alpha]_D^{30} = +10.8$ (*c* 0.5, C_6D_6); IR ν_{max} (film) 2940, 2900, 2830, 1445, 1350 (asymmetric S=O), (symmetric S=O) 1150 cm^{-1}; ^1H NMR (C_6D_6) δ 4.59 (2H, d, *J* 6.5 Hz, OC*H*HO), 4.49 (2H, d, *J* 6.5 Hz, OCH*H*O), 4.14 (2H, q, *J* 11.0, 5.0 Hz, OCH), 3.22 (6H, s, OMe), 2.89 (2H, dd, *J* 11.0, 5.0 Hz, NC*H*H), 2.81 (2H, t, NCH_2CH_2), 2.66 (3H, s, SO_2Me), 2.61 (2H, m, NCH*H*), 2.54 (2H, m, NCH_2CH_2); ^{13}C NMR (C_6D_6) δ 96.6 (OCH_2O), 82.1 (OCH), 72.6 (NCH_2CH_2), 68.6 (NCH_2CH_2), 59.4 (NCH_2CHO), 55.9 (OMe), 37.9 (SO_2Me); $LRMS_{EI}$ *m/e* (rel. intensity %) 313 (M^+, 3), 303 (13), 218 (100), 204 (39), 188 (7), 174 (15), 160 (7) and 130 (7).

CAUTION: All reactions employing azides were conducted in a fume-hood with a lowered sash and a reinforced blast-shield. Where it was necessary to conduct certain azide displacements on a multigram scale, the appropriate precautions necessary for large scale working with explosive reagents were observed. Caution must also be exercised when recording melting points because detonation sometimes occurs.

4.1.7. (3*S*,4*S*)-1-(2-Azidoethyl)-3,4-bis(methoxymethyloxy)-pyrrolidine 9. To a stirred solution of pyrrolidine **8** (15.6 g, 49.8 mmol) in dry dimethylformamide (60 mL) at 20 °C under an atmosphere of dry nitrogen was added sodium azide (6.47 g, 99.6 mmol; CAUTION) using a solid-addition funnel equipped with a side-arm. The mixture was slowly heated (CAUTION) to 80 °C and stirring continued for 16 h at 80 °C (CAUTION) under an atmosphere of dry nitrogen. DMF was then removed by co-evaporation under reduced pressure with toluene (50 mL, repeated twice) at 20 °C. The residue was partitioned with water (90 mL) and ethyl acetate (100 mL), the layers separated and the aqueous layer extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (2×50 mL) and dried over $MgSO_4$. The solution was filtered through a sintered glass funnel and the filtrate was evaporated. The residue was adsorbed onto neutral alumina and the impregnated dispersion was applied to the top of a pre-packed column of silica gel and eluted with 1:1 diethyl ether/40–60 °C petroleum ether. The appropriate fractions were combined, filtered through a glass wool plug and the eluent was evaporated under reduced pressure to give **9** (7.0 g, 54%); $[\alpha]_D^{32} = +1.9$ (*c* 2.1, chloroform); IR ν_{max} (film) 2935, 2890, 2800, 2100 (azide), 1470 cm^{-1}; ^1H NMR δ 4.72 (2H, d, *J* 6.5 Hz, OC*H*HO), 4.65 (2H, d, *J* 6.5 Hz, OCH*H*O), 4.15 (2H, dt, *J* 4.5, 1.5 Hz, OCH), 3.39 (6H, s, OMe), 3.39 (2H, t, *J* 2.5 Hz, NCH_2CH_2), 3.01 (2H, dd, *J* 9.5, 5.5 Hz, NC*H*H), 2.71 (2H, m, NCH_2CH_2), 2.63 (2H, dd, *J* 9.5, 4.5 Hz, NCH*H*); ^{13}C NMR δ 95.8 (OCH_2O), 81.4 (OCH), 59.0 (NCH_2CHO), 55.5 (OMe), 54.8 (NCH_2CH_2), 49.8 (NCH_2CH_2); $LRMS_{EI}$ *m/e* (rel. intensity %) 261 ($[M+H]^+$, 12), 261 (M^+, 3), 204 (100), 160 (10), 99 (24), 82 (50). $HRMS_{EI}$ Calcd for $C_{10}H_{20}N_4O_4$ (M^+) 260.1485. Found: 260.1494.

4.1.8. Procedure D: (3*S*,4*S*)-1-(2-aminoethyl)-3,4-bis-(methoxymethyloxy)pyrrolidine 10. To a three-necked 100 mL flask equipped with a two-way vacuum tap, rubber septum and magnetic stirring bar were added pyrrolidine **9** (6.88 g, 26.5 mmol), ethanol (50 mL) and 10% palladium on carbon (2.0 g). The vessel was cooled to 0 °C, evacuated to 15 mmHg and purged with a hydrogen at positive atmospheric pressure. Following three successive cycles of evacuation-purging the vessel was allowed to warm to 20 °C and stirring was continued for 16 h at that temperature under fresh hydrogen at positive atmospheric pressure. (Monitoring by IR spectroscopy showed the absence of ν_{max} 2100 cm^{-1} azide stretch). The mixture was filtered through a fluted paper and washed with ethanol (4×5 mL). The filtrates were evaporated and the residue was adsorbed onto neutral alumina. The impregnated dispersion was applied to the top of a pre-packed flash column of silica gel and eluted with 199:1 methanol/0.880 aqueous ammonia. The appropriate fractions were combined, filtered through a fluted paper and the eluent was evaporated. The residue was dissolved in THF (50 mL) and dried over K_2CO_3. The solution was filtered through a fluted paper and evaporated to give **10** (5.1 g, 82%) as a pale yellow oil. An analytical sample was obtained by preparative silica plate thin-layer chromatography (with 99:1 acetonitrile/0.880 aqueous ammonia followed by extraction and isolation as in General procedure B) to give **10** as an oil; $[\alpha]_D^{33} = +2.0$ (*c* 1.4, chloroform); IR ν_{max} (film) 3420 (NH), 2935, 2895, 2825 cm^{-1}; ^1H NMR δ 4.74 (2H, d, *J* 6.5 Hz, OC*H*HO), 4.65 (2H, d, *J* 6.5 Hz, OCH*H*O), 4.13 (2H, t, *J* 4.2 Hz, OCH), 3.38 (6H, s, OMe), 2.95 (2H, dd, *J* 9.5, 6.0 Hz, NC*H*H), 2.81 (2H, t, *J* 6.5 Hz, NCH_2CH_2), 2.57 (2H, dd, *J* 10.0, 4.5 Hz, NCH*H*), 2.56 (2H, m, NCH_2CH_2), 1.90 (2H, br s, CH_2NH_2); ^{13}C NMR δ 95.7 (OCH_2O), 81.5 (OCH), 58.9 ($OCHCH_2N$ and NCH_2CH_2), 55.4 (OMe), 40.2 (NCH_2CH_2); $LRMS_{EI}$ *m/e* (rel. intensity %) 235 ($[M+H]^+$, 14), 218 (6), 204 (100), 160 (9), 111

(6), 98 (15), 82 (27), 68 (15). $HRMS_{EI}$ Calcd for $C_{10}H_{22}N_2O_4$ (M^+) 234.1580. Found: 234.1588.

4.1.9. (3*S*,4*S*)-1-(2-Aminoethyl)pyrrolidine-3,4-diol 11. Hydrochloric acid (25 mL, 10 M) was added dropwise to a stirred solution of **10** (5.0 g, 21.4 mmol) in methanol (25 mL) at 0 °C under an atmosphere of nitrogen. The mixture was allowed to warm slowly to 20 °C with stirring for 16 h under an atmosphere of nitrogen. Evaporation gave a residue that was made alkaline with 4 M potassium hydroxide in methanol (4 M, CAUTION) at 0 °C while stirring under an atmosphere of nitrogen. The mixture was allowed to warm slowly to 20 °C with stirring for 2 h under an atmosphere of nitrogen. Evaporation gave a residue that was suspended in saturated aqueous ammonium chloride (45 mL) and then continuously extracted with chloroform for 96 h under an atmosphere of nitrogen. The organic layer was dried over K_2CO_3, filtered and evaporated. Fractional distillation of the residue at 160–180 °C/2.0 mmHg gave an oil that was adsorbed onto neutral alumina and the impregnated dispersion applied to the top of a pre-packed flash column of silica gel and eluted with 1:49 0.880 ammonia/methanol. The appropriate fractions were combined, filtered and evaporated. The residue was dissolved in THF (45 mL) and dried over K_2CO_3. Filtration and evaporation gave **11** (1.59 g, 10.9 mmol, 51%) as an oil. An analytical sample was obtained by preparative alumina thin-layer chromatography (with methanol at 5 °C in the dark over 16 h followed by extraction and isolation as in General procedure B) to give **11** as an opaque, waxy solid; $[\alpha]_D^{33} = +22.2$ (*c* 7.1, methanol); IR ν_{max} (film) 3298, 2935, 2820 cm^{-1}; ^1H NMR (250 MHz, CD_3OD) δ 4.82 (4H, br s, CHO*H*×2, CH_2NH_2), 4.00 (2H, m, C*H*OH), 2.93 (2H, dd, *J* 10.5, 6.0 Hz, NC*H*H), 2.70 (2H, t, *J* 6.5 Hz, CH_2NH_2), 2.53 (2H, m, $NCH_2CH_2NH_2$), 2.47 (2H, dd, *J* 10.5, 5.0 Hz, NCH*H*); ^{13}C NMR δ 79.1 (*C*HOH), 61.8 (NCH_2CHOH), 53.7 ($NCH_2CH_2NH_2$), 40.8 ($NCH_2CH_2NH_2$); $LRMS_{EI}$ *m*/*e* (rel. intensity %) 147 (75), 130 (44), 116 (100), 104 (20), 98 (10), 85 (8), 72 (12), 58 (14). $LRMS_{FAB}$ *m*/*e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 147 ($[M+H]^+$, 100), 146 (M^+, 4), 145 (45), 133 (5), 130 (21), 116 (41). $HRMS_{FAB}$ Calcd for $C_6H_{15}N_2O_2$ $[M+H]^+$ 147.1134. Found: 147.1129.

4.1.10. (3*S*,3′*S*,4*S*,4′*S*)-3′,4′-Bis(methoxymethyloxy)-1,1′-ethylenedipyrrolidine-3,4-diol 12. To a stirred suspension of methanesulfonate **6** (3.89 g, 10.6 mmol), potassium hydrogen carbonate (3.19 g, 31.9 mmol), 18-crown-6 (0.28 g, 1.1 mmol) and potassium iodide (0.18 g, 1.1 mmol) in dry dimethylformamide (40 mL) at 0 °C under an atmosphere of dry nitrogen was added via a syringe a solution of pyrrolidinediol **11** (1.55 g, 10.6 mmol) in dry triethylamine (2 mL) in one portion. The mixture was allowed to warm slowly to 100 °C and stirring was continued for 48 h at that temperature under an atmosphere of dry nitrogen. Removal of DMF by vacuum distillation (45–60 °C/2–3 mmHg), addition of saturated aqueous ammonium chloride (35 mL) and continuous extraction with ethyl acetate for 48 h gave an organic layer that was dried over K_2CO_3, filtered and evaporated to give a residue that was adsorbed onto neutral alumina and the impregnated dispersion applied to the top of a pre-packed flash column of silica gel and eluted with 7:3 chloroform/methanol. The appropriate fractions were combined, filtered and evaporated. To the residue was added dichloromethane and the solution was filtered through a fluted paper and evaporated to give **12** (1.05 g, 31%) as an oil. An analytical sample was obtained by preparative silica plate thin-layer chromatography (five plate elutions with 19:1 chloroform/methanol followed by extraction and isolation as in General procedure B) to give **12** as a clear oil; $[\alpha]_D^{32} = +14.7$ (*c* 0.18, chloroform); IR ν_{max} (film) 3365 (OH), 2900, 2825 cm^{-1}; ^1H NMR δ 4.72 (2H, d, *J* 6.5 Hz, OC*H*HO), 4.65 (2H, d, *J* 6.5 Hz, OCH*H*O), 4.22 (2H, m, C*H*OMOM), 4.15 (2H, m, C*H*OH), 3.82 (2H, br s, CHO*H*), 3.39 (6H, s, OMe), 3.19 (2H, dd, *J* 10.0, 5.0 Hz, NC*H*H), 3.02 (2H, dd, *J* 10.0, 5.0 Hz, NCH*H*), 2.70 (8H, br m, $N'CH_2$×2 and NCH_2CH_2N'); ^{13}C NMR δ 95.8 (OCH_2), 81.0 (CHOH), 77.3 (*C*HOMOM), 60.2 (MOM/*C*H_2N), 59.0 (HO/*C*H_2N), 55.7 (OMe), 53.8 (CH_2CH_2); $LRMS_{FAB}$ *m*/*e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 321 ($[M+H]^+$, 100), 303 (46), 278 (83), 218 (46), 204 (35) 174 (10), 130 (66), 116 (31). $HRMS_{FAB}$ Calcd for $C_{14}H_{29}N_2O_6$ $[M+H]^+$ 321.2026. Found: 321.2032.

4.1.11. (3*S*,3′*S*,4*S*,4′*S*)-3,4-Bis(methanesulfonyloxy)-3′,4′-bis-(methoxymethyloxy)-1,1′-ethylenedipyrrolidine 13. To a stirred solution of pyrrolidine-3,4-diol **12** (1.02 g, 3.19 mmol) and triethylamine (0.97 g, 9.6 mmol) in dry dichloromethane (40 mL) at 0 °C under an atmosphere of dry nitrogen was added dropwise a solution of methanesulfonyl chloride (1.10 g, 9.57 mmol) in dichloromethane (15 mL) using a stainless steel double-tipped needle. The mixture was allowed to warm slowly to 20 °C and stirring was continued for 45 min at that temperature under an atmosphere of dry nitrogen. The mixture was quenched by the addition of water (35 mL), and worked up and the residue purified by column chromatography as in General procedure C but using 19:1 chloroform/methanol to give **13** (0.70 g, 46%) as a wax. An analytical sample was obtained by preparative silica plate thin-layer chromatography (four plate elutions with 199:1 chloroform/methanol at 20 °C in the dark) to give **13** as a clear wax; $[\alpha]_D^{33} = +26.2$ (*c* 0.93, chloroform); IR ν_{max} (film) 2940, 2895, 2820, 1360 (asymmetric S=O), 1175 (symmetric S=O) cm^{-1}; ^1H NMR δ 5.14 (2H, t, *J* 3.5 Hz, MsOCH), 4.70 (2H, d, *J* 7.3 Hz, OC*H*HO), 4.64 (2H, d, *J* 7.3 Hz, OCH*H*O), 4.12 (2H, t, *J* 4.0 Hz, MOMOC*H*), 3.39 (6H, s, OMe), 3.15 (2H, dd, *J* 10.0, 6.0 Hz, Ms/C*H*HN), 3.10 (6H, s, SO_2Me), 2.96 (2H, dd, *J* 10.0, 6.0 Hz, MsCH*H*N), 2.82 (2H, dd, *J* 10.0, 4.0 Hz, MOM/C*H*HN), 2.62 (4H, m, CH_2CH_2), 2.57 (2H, dd, *J* 10.0, 4.0 Hz, MOMCH*H*N); ^{13}C NMR δ 95.8 (OCH_2O), 82.4 (MsOCH), 81.4 (MOMO*C*H), 59.3 (Ms/*C*H_2N), 58.6 (MOM/*C*H_2N), 55.6 (OMe), 54.4 (NCH_2CH_2N'), 53.8 (NCH_2CH_2N'), 38.5 (SO_2Me); $LRMS_{FAB}$ *m*/*e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 477 ($[M+H]^+$, 34), 476 (M^+, 3), 286 (24), 272 (6), 218 (28) 204 (100), 174 (9). $HRMS_{FAB}$ Calcd for $C_{16}H_{33}N_2O_{10}S_2$ $[M+H]^+$ 477.1577. Found: 477.1569.

4.1.12. (3*R*,3′*S*,4*R*,4′*S*)-3,4-Diazido-3′,4′-bis(methoxymethyloxy)-1,1′-ethylenedipyrrolidine 14. To a stirred solution of dipyrrolidine **13** (0.69 g, 1.45 mmol) in dry DMF (7 mL) at 20 °C under an atmosphere of dry nitrogen was added portionwise lithium azide (0.706 g, 14.4 mmol; CAUTION) using a solid-addition funnel equipped with a side-arm. The mixture was slowly heated to 80 °C (CAUTION) and stirring continued for 48 h at 80 °C (CAUTION) under an atmosphere of dry nitrogen. Aqueous lithium chloride (25 mL, 2 M) was added and the mixture was continuously extracted with diethyl ether for 96 h. The organic layer was dried over $MgSO_4$, filtered and evaporated The crude product was adsorbed onto silica gel and the impregnated dispersion applied to the top of a pre-packed flash column. This material was purified by flash column chromatography over silica gel (9:1 ethyl acetate/40–60 °C petroleum ether) to give **14** (0.30 g, 56%) as a white powder, mp 43 °C. An analytical sample was obtained by preparative silica plate thin-layer chromatography (three plate elutions with 4:1 ethyl acetate/40–60 °C petroleum ether) to give a grey powder that was recrystallised from chloroform by the slow diffusion of *n*-hexane vapour at 5 °C to give **14** as prisms, mp 48–49 °C; $[\alpha]_D^{34} = -6.0$ (*c* 0.2, chloroform); IR ν_{max} (film) 2935, 2800, 2804, 2100 (azide) cm^{-1}; ^1H NMR δ 4.72 (2H, d, *J* 6.0 Hz, OC*H*-HO), 4.64 (2H, d, *J* 6.0 Hz, OCH*H*O), 4.12 (2H, t, *J* 4.0 Hz, MOMOC*H*), 3.86 (2H, t, *J* 3.6 Hz, N_3CH), 3.38 (6H, s, OMe), 3.00 (4H, m, MOMOC*H*CH_2), 2.62 (8H, m, N_3CHCH_2×2 and CH_2CH_2); ^{13}C NMR 95.8 (OCH_2O), 81.4 (MOMO*C*H), 65.7 (N_3CH), 59.3 (MOMOCH*C*H_2), 58.1 (N_3CHCH_2), 55.6 (OMe), 54.7 (NCH_2CH_2N/MOM), 53.9 (NCH_2CH_2N/MOM); $LRMS_{FAB}$ *m/e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 371 ($[M+H]^+$, 100), 285 (18), 218 (28), 204 (67), 180 (15) 154 (17) and 136 (18). $HRMS_{FAB}$ Calcd for $C_{14}H_{27}N_8O_4$ $[M+H]^+$ 371.2155. Found: 371.2142.

4.1.13. (3*R*,3′*S*,4*R*,4′*S*)-3,4-Diamino-3′,4′-bis(methoxymethyloxy)-1,1′-ethylenedipyrrolidine 15. Prepared according to the General procedure D, using dipyrrolidine **14** (0.277 g, 0.75 mmol) with purification by flash column chromatography on silica gel (49:1 methanol/0.88 aqueous ammonia) to give a residue that was dissolved in dry THF (20 mL) and the solution stirred over KOH pellets, filtered and evaporated to give **14** (0.174 g, 73%) as a yellow oil. An analytical sample was obtained by preparative silica plate thin-layer chromatography (three plate elutions with 99:1 methanol/0.88 aqueous ammonia at 20 °C in the dark) to give **15** as a clear oil that turned cloudy on exposure to air; $[\alpha]_D^{33} = -9.7$ (*c* 1.1, chloroform); IR ν_{max} (KBr) 3340 (asymmetric NH), 3290 (symmetric NH), 2930, 2895, 2820 cm^{-1}; ^1H NMR δ 4.70 (2H, d, *J* 6.5 Hz, OC*H*HO), 4.62 (2H, d, *J* 6.5 Hz, OCH*H*O), 4.11 (2H, m, MOMOC*H*), 3.35 (6H, s, OMe), 3.20–2.30 (18H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 95.6 (OCH_2O), 81.2 (MOMO*C*H), 61.3 (H_2NCH), 59.5 (MOMOCH*C*H_2), 59.1 (H_2NCHCH_2), 55.6 (OMe), 54.5 (NCH_2CH_2N'), 54.1 (NCH_2CH_2N'); $LRMS_{FAB}$ *m/e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 319 ($[M+H]^+$, 28), 235 (10), 218 (65), 204 (100), 174 (15), 136 (20). $HRMS_{FAB}$ Calcd for $C_{14}H_{30}N_4O_4$ $[M+H]^+$ 319.2345. Found: 319.2335.

4.1.14. (3*R*,3′*S*,4*R*,4′*S*)-3,4-Diamino-1,1′-ethylenedipyrrolidine-3′,4′-diol 16. To a stirred solution of **15** (0.152 g, 0.48 mmol) in methanol (2 mL) at 0 °C concd hydrochloric acid (2 mL, 10 M) was added dropwise. The mixture was allowed to warm slowly to 20 °C and stirring continued at that temperature for 16 h. Evaporation gave a residue that was made basic by the addition of *N*,*N*-dimethylethylamine (CAUTION) at 0 °C, which was stirred for an additional 30 min under an atmosphere of nitrogen. Evaporation gave a residue that was adsorbed onto neutral alumina and the impregnated dispersion then applied to the top of a pre-packed alumina column and eluted with 9:1 water/0.880 aqueous ammonia. The appropriate fractions were combined, filtered and evaporated to give **16** (11 mg, 10%) as a brown gum. An analytical sample was obtained by preparative silica plate thin-layer chromatography (five plate elutions with 19:1 0.880 aqueous ammonia/methanol eluted at 5 °C in the dark). Bands were continuously extracted with THF for 24 h in a micro-soxhlet thimble. The organic extract was dried over KOH pellets, filtered and evaporated to give **16** as an oil; IR ν_{max} (thin film) 3355 (br, NH, OH), 1448, 1379 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 4.57 (2H, d, *J* 3.0 Hz, C*H*OH), 4.17 (2H, t, *J* 5.0 Hz, C*H*NH_2), 3.94 (2H, m, HOCHC*H*HN), 3.66 (4H, m, HOCHCH*H*N and N′CH_2CH_2N), 3.47 (2H, dd, *J* 10.0, 6.0 Hz, $H_2NCHCHHN$), 3.18 (2H, m, N′CH_2CH_2N), 3.00 (2H, dd, *J* 10.0, 4.0 Hz, $H_2NCHCHHN$); ^{13}C NMR (150 MHz, D_2O) δ 77.2 (CHOH), 62.2 (H_2NCH), 58.7 (HOCH*C*H_2), 58.0 (H_2NCHCH_2), 56.2 (HO/NCH_2CH_2N), 51.4 (HO/NCH_2CH_2N); $LRMS_{FAB}$ *m/e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 231 ($[M+H]^+$, 74), 192 (37), 176 (43), 171 (35), 154 (70) 149 (100), 136 (77), 121 (19), 107 (46). $HRMS_{FAB}$ Calcd for $C_{10}H_{23}N_4O_2$ $[M+H]^+$ 231.1821. Found: 231.1838.

4.1.15. (4*S*,5*S*)-4,5-Bis[methyl(methanesulfonyloxy)]-2,2-dioxo-1,2,3-thiolane 19. To a stirred solution of dimethanesulfonate **18**[16] (2.30 g, 7.10 mmol) and sodium periodate (2.28 g, 10.7 mmol) in 5:3 acetonitrile/water (60 mL) at 0 °C was added ruthenium(IV) oxide (15 mg, 0.11 mmol) followed by the portionwise addition of water (50 mL, kept near 0 °C with ice) to control the highly exothermic reaction. Stirring was continued at 20 °C for 2 h. The mixture was extracted with ethyl acetate (60 mL), the organic layer separated and kept. The aqueous layer was further with extracted ethyl acetate (3×50 mL) and the combined organic layers (including the originally separated layer) were washed with brine (2×40 mL) and dried over $MgSO_4$. The solution was filtered, evaporated and the residue dissolved in dichloromethane (minimum volume) and applied to the top a column of silica gel. Flash chromatography using 1:1 ethyl acetate/40–60 °C petroleum ether afforded **19** (1.04 g, 43%) as a grey powder, mp 89–91 °C. An analytical sample crystallised from 1:1 ethyl acetate/40–60 °C petroleum ether as white prisms, mp 90–91 °C; $[\alpha]_D^{30} = -48.3$ (*c* 0.9, acetone); IR ν_{max} (chloroform), 1340 (asymmetric S=O), 1180 (symmetric S=O)

cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.41 (2H, m, OSCH), 4.75 (2H, dd, J 12.0, 1.0 Hz, C*H*HOMs), 4.64 (2H, dd, J 12.0, 6.0 Hz, CH*H*OMs), 3.29 (6H, s, SO_2Me); ^{13}C NMR (DMSO-d_6) δ 80.4 (OSCH), 66.7 (CH_2OMs), 37.3 (SO_2Me); $LRMS_{FAB}$ *m/e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 363 ([M+Na]$^+$, 94), 344 (22), 329 (47), 307 (37), 286 (100), 245 (26), 234 (36), 216 (31), 202 (31). $HRMS_{FAB}$ Calcd for $C_6H_{12}NaO_{10}S_3$ [M+Na]$^+$ 362.9490. Found: 362.9465.

4.1.16. (2*S*,3*R*)-3-Azido-1,4-bis(methanesulfonyloxy)-butane-2-ol 20. To a stirred solution of sulfone **19** (0.90 g, 2.91 mmol) in 1:1 acetone/water (30 mL) at 0 °C was added sodium azide (0.95 g, 14.6 mmol; CAUTION) in one portion. The mixture was allowed to warm slowly to 20 °C and stirring was continued at that temperature for 16 h. When the sulfone had been consumed (as shown by $KMnO_4$ staining of TLC plate followed by heating) the solution was concentrated and a 1:1 mixture of 4 M sulfuric acid/diethyl ether (30 mL) was added (CAUTION: any inorganic azide will be converted into hydrazoic acid, which represents a serious explosion hazard). Stirring was continued at 20 °C for 16 h. The organic layer was separated and kept. The aqueous layer was extracted with ethyl acetate (3×30 mL) and the combined organic layers (including the originally separated layer) were washed with brine (2×25 mL) and dried over Na_2SO_4. The solution was filtered, evaporated and the residue was absorbed onto a small portion of silica gel and applied to the top a column of silica gel. Flash chromatography using 1:1 ethyl acetate/40–60 °C petroleum ether afforded **20** (0.59 g, 67%) as a clear, mobile liquid; $[\alpha]_D^{30} = -35.4$ (c 0.6, chloroform); IR ν_{max} (film) 3515 (OH), 3030, 2940, 2105 (azide) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.61 (1H, dd, J 12.0, 3.5 Hz, $_1$C*H*HOMs), 4.46 (1H, m, C*H*OH), 4.39 (1H, m, CHN_3), 4.36 (1H, dd, J 12.0, 5.0 Hz, $_1$CH*H*OMs), 3.90 (1H, m, C*H*HOMs), 3.83 (1H, m, CH*H*OMs), 3.3 (1H, br s, CHO*H*), 3.11 (6H, s, SO_2Me); ^{13}C NMR ($CDCl_3$) δ 70.5 ($_1C$H$_2$OMs), 68.4 (CHOH), 68.3 ($_4C$H$_2$OMs), 60.8 (CHN_3), 36.7 (SO_2Me); $LRMS_{FAB}$ *m/e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 436 ([M+Cs]$^+$, 100), 326 ([M+Na]$^+$, 30), 304 ([M+H]$^+$, 43), 288 (16), 278 (63), 208 (23), 198 (72), 180 (80), 168 (26); $HRMS_{FAB}$ Calcd for $C_6H_{14}N_3O_7S_2$ [M+H]$^+$ 304.0273. Found: 304.0250.

4.1.17. (3*R*,3′*R*,4*S*,4′*S*)-3,3′-Diazido-1,1′-ethylenedipyrrolidine-4,4′-diol 21. To a stirred suspension of azide **20** (0.55 g, 1.80 mmol), potassium hydrogen carbonate (0.54 g, 5.4 mmol) and 18-crown-6 (48 mg, 0.18 mmol) in dry DMF (8 mL) at 0 °C under an atmosphere of dry nitrogen was added via a syringe a solution of ethylenediamine (60 mg, 0.90 mmol) in dry pyridine (0.5 mL). The mixture was allowed to warm slowly to 80 °C (CAUTION) and stirring continued for 72 h at that temperature under an atmosphere of dry nitrogen. DMF was then removed by co-evaporation under reduced pressure with benzene (10 mL, repeated three times) at 20 °C. The residue was continuously extracted with THF for 48 h in a micro-soxhlet thimble under an atmosphere of nitrogen for 48 h. The organic layer was dried over K_2CO_3, filtered and evaporated The residue was adsorbed onto basic alumina and the impregnated dispersion was applied to the top of a column of silica gel that was eluted with 4:1 chloroform/methanol. Evaporation of the appropriate fractions gave a residue that was dissolved in THF (15 mL) and stirred over K_2CO_3. The solution was filtered and evaporated to give **21** (61 mg, 12%) as a clear wax. An analytical sample was obtained by preparative silica plate thin-layer chromatography (three plate elutions with 19:1 chloroform/methanol eluted at 5 °C in the dark). Extraction and isolation as in General procedure B, but using THF in place of chloroform, afforded **21** as a wax; $[\alpha]_D^{28} = +44.7$ (c 1.2, methanol); IR ν_{max} (solid film) 3385 (OH), 2930, 2850, 2110 (azide) cm^{-1}; ^{1}H NMR (CD_3OD) 4.77 (2H, s, CHO*H*), 4.39 (2H, q, J 5.0 Hz, C*H*OH), 3.90 (2H, q, J 5.0 Hz, CHN_3), 3.05 (4H, m, $_{Pyr}H_{2,2',5,5'\text{-}cis}$), 2.77 (4H, s, CH_2CH_2), 2.75 (4H, m, $_{Pyr}H_{2,2',5,5'\text{-}trans}$); ^{13}C NMR (151 MHz, CD_3OD) δ 72.6 (CHOH), 63.0 (CHN_3), 60.4 ($_{Pyr}C_{5,5'}$), 57.3 ($_{Pyr}C_{2,2'}$), 55.2 (CH_2CH_2); $LRMS_{FAB}$ *m/e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX) 283 ([M+H]$^+$, 100), 251 (97), 172 (26), 163 (10), 155 (37), 149 (18), 141 (79), 136 (36), 122 (33); $HRMS_{FAB}$ Calcd for $C_{10}H_{19}N_8O_2$ [M+H]$^+$ 283.1631. Found: 283.1617.

4.1.18. (3*R*,3′*R*,4*S*,4′*S*)-3,3′-Diamino-1,1′-ethylenedipyrrolidine-4,4′-diol 22. Diazide **21** (48 mg, 0.17 mmol) was subjected to hydrogenolysis according to General procedure D. (On completion, IR spectroscopy showed the absence of ν_{max} 2100 cm^{-1} azide stretch.) The mixture was filtered through a micro sintered glass funnel packed with a small quantity of Celite 545 and washed with ethanol (4×2 mL). The filtrates were evaporated and the residue adsorbed onto basic alumina and the impregnated dispersion was applied to the top of a pre-packed column of alumina and eluted with 9:9:2 methanol/water/0.880 aqueous ammonia. The appropriate fractions were combined, filtered through a fluted paper and the eluent evaporated. The residue was dissolved in 3:1 THF/methanol and dried over K_2CO_3. The solution was filtered through a fluted paper and evaporated to give **22** (9 mg, 23%) as a brown gum. An analytical sample was obtained by preparative alumina plate thin-layer chromatography (four plate elutions with 19:1 methanol/0.880 ammonia eluted at 5 °C in the dark). The residue was continuously extracted with THF for 48 h in a micro-soxhlet thimble under an atmosphere of nitrogen. The organic layer was dried over KOH pellets, filtered and evaporated to give **22** as light tan solid; $[\alpha]_D^{32} = +36.3$ (c 0.13, methanol); IR ν_{max} (thin film) 3420 (OH), 2960, 2850 cm^{-1}; ^{1}H NMR (CD_3OD) δ 4.03 (2H, m, C*H*OH), 3.27 (2H, m, C*H*NH$_2$), 3.04 (2H, dd, J 10.0, 5.5 Hz, $_{Pyr}H_{5,5'\text{-}cis}$), 2.91 (2H, dd, J 10.0, 7.0 Hz, $_{Pyr}H_{2,2'\text{-}cis}$), 2.59 (4H, s, CH_2CH_2), 2.50 (2H, dd, J 10.0, 5.0 Hz, $_{Pyr}H_{5,5'\text{-}trans}$), 2.35 (2H, dd, J 10.0, 1.0 Hz, $_{Pyr}H_{2,2'\text{-}trans}$); NOESY spectrum showed correlations of δ 4.03 with δ 3.27, 3.04 and 2.50; of δ 3.27 with δ 3.04, 2.91 and 2.35; of δ 3.04 with δ 2.59 and 2.50; of δ 2.91 with δ 2.59 and 2.35; of δ 2.59 with δ 2.50, 2.35; and of δ 2.50 with δ 2.35; ^{13}C NMR (62 MHz, CD_3OD) δ 71.7 (CHOH), 62.6 ($_{Pyr}C_{5,5'}$), 60.8 ($_{Pyr}C_{2,2'}$), 56.1 (CH_2CH_2), 54.5 ($CHNH_2$); $LRMS_{FAB}$ *m/e* (rel. intensity %; +ve *m*-$NO_2C_6H_5CO_2H$ MATRIX)

231 ([M+H]$^+$, 32), 192 (48), 176 (47), 171 (27), 154 (93), 149 (34), 136 (100), 120 (22) and 107 (57). $HRMS_{FAB}$ Calcd for $C_{10}H_{23}N_4O_2$ [M+H]$^+$ 231.1821. Found: 231.1838.

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18. Crystal data for **1a**. $C_{10}H_{20}N_2O_4$, $M_r = 232.28$, monoclinic space group *Cm*, $T = 150$ K, $a = 11.192(2)$, $b = 7.332(2)$, $c = 13.945(3)$ Å, $\beta = 96.08(3)°$, $U = 1137.9(4)$ Å^3, $Z = 4$, $D_c = 1.356$ g cm^{-3}, $\mu = 0.104$ mm^{-1}, $F(0\,0\,0) = 504$, crystal size 0.4×0.1×0.1 mm, 1483 unique data were produced from 8044 measured reflections ($R_{int} = 0.1042$), 151 parameters refined to $R_1 = 0.0652$ and $wR_2 = 0.1982$ [$I > 2\sigma(I)$] ($R_1 = 0.0761$ and $wR_2 = 0.2563$ for all data), with residual electron densities of 0.407 and −0.395 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure of **1a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 218589. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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